(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068253 A1

(51) International Patent Classification[7]: A61K 38/12, 31/535, 31/353, 31/405, 9/51, A61P 27/02

(21) International Application Number: PCT/EP03/01369

(22) International Filing Date: 12 February 2003 (12.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02003432.8 14 February 2002 (14.02.2002) EP

(71) Applicant *(for all designated States except US)*: **MERCK PATENT GMBH** [DE/DE]; Frankfurter Strasse 250, D-6493 Darmstadt (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BENDER, Hans-Markus** [DE/DE]; Rosenheimerstrasse 19, 83104 Ostermünchen (DE). **LANG, Ulrich** [DE/DE]; Haydnweg 11, D-64646 Heppenheim (DE). **WIESNER, Matthias** [DE/DE]; Beethovenring 10, D-64342 Seeheim-Jugenheim (DE). **FRIEDLANDER, Martin** [US/US]; 1720 Zapo Street, Del Mar, CA 92014 (US).

(74) Common Representative: **MERCK PATENT GMBH**; Frankfurter Strasse 250, D-64293 Darmstadt (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/068253 A1

(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF EYE DISEASES

(57) Abstract: Method and compositions for prophylaxis and/or treatment of diseases of the eye using antagonists of the integin receptors $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. The compositions can be nanoparticles and are administered to the eye by injection into the subTenon's space of the eye.

TECHNICAL FIELD

The present invention relates generally to the field of medicine, and relates specifically to methods and compositions for the prophylaxis and/or treatment of diseases of the eye using antagonists of the integin receptors $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. More specifically, the invention relates to methods and compositions for the prophylaxis and/or treatment of diseases of the eye using antagonists of the integrin receptors $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ wherein the compositions are administered to the eye by subTenon's injection.

BACKGROUND

Integrins are a class of cellular receptors known to bind extracellular matrix proteins, and therefore mediate cell-cell and cell-extracellular matrix interactions, referred generally to as adhäsion events. Integrins receptors constitute a family of proteins across membranes with shared structural characteristics heterodimeric glycoprotein complexes formed of α and β subunits.

One class of integrin receptors, the vitronectin receptor, named for its original characteristic of preferential binding to vitronectin, is known to refer to three different integrins, designated. $\alpha_v\beta_1$, $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Horton, Int. J. Exp. Pathol., 71:741-759 (1990). $\alpha_v\beta_1$ binds fibronectin and vitronectin. $\alpha_v\beta_3$ binds a large variety of ligands, including fibrin, fibrinogen, laminin, thrombospondin, vitronectin, von Willebrand's factor, osteospontin and bone sialoprotein I. $\alpha_v\beta_5$ binds vitronectin. The specific cell adhesion roles these three integrins play in the many cellular interactions in tissues is still under investigation, but it is clear that there are different integrins with different biological functions.

One important recognition site in the ligand for many integrins is the arginine-glycine-aspartic acid (RGD) tripeptide sequence. RGD is found in all of the ligands identified above for the vitronectin receptor integrins. This RGD recognition site can be mimicked by polypeptides ("peptides") that contain the RGD sequence, and such RGD peptides are known inhibitors of integrin function.

Integrin inhibitors containing the RGD sequence are disclosed, for example, in EP 0 770 622 A2. The compounds described inhibit in particular the interactions of β_3- and/or β_5-integrin receptors with ligands and are particularly active in the case of the integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $a_{II}\beta_3$, but also relative to $\alpha_v\beta_1$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$ receptors. These actions can be demonstrated, for example, according to the method described by J. W. Smith et al. in J. Biol. Chem. 265, 12267-12271 (1990). In addition, the compounds possess anti-inflammatory effects.

On basis of integrin inhibitors containing the RGD sequence a multitude of antagonists without the RGD sequence have been made available. Those integrin inhibitors without RGD sequence are disclosed, for example, in WO 96/00730 A1, WO 96/18602 A1, WO 97/37655 A1, WO 97/06791 A1, WO 97/45137 A1, WO 97/23451 A1, WO 97/23480 A1, WO 97/44333 A1, WO 98/00395 A1, WO 98/14192 A1, WO 98/30542 A1, WO 99/11626 A1, WO 99/15178 A1, WO 99/15508 A1, WO 99/26945 A1, WO 99/44994 A1, WO 99/45927 A1, WO 99/50249 A2, WO 00/03973 A1, WO 00/09143 A1, WO 00/09503 A1, WO 00/33838 A1.

DE 1970540 A1 disclose bicyclic aromatic amino acids acting as integrin inhibitors of the α_v integrin receptors, particulary of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. The compounds are very particularly active as adhesion receptor

antagonists for the vitronectin receptor $\alpha_v\beta_3$. This effect can be demonstrated, for example, by the method described by J.W. Smith et al. in J. Biol. Chem. 265, 11008-11013 and 12267-12271 (1990).

WO 00/26212 A1 discloses chromenone and chromanone derivatives acting as integrin inhibitors of the α_v integrin receptors, particulary of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. The compounds are also very particularly active as adhesion receptor antagonists for the vitronectin receptor $\alpha_v\beta_3$.

Integrin inhibitors have been suggested as pharmaceutically active principle in human and veterinary medicine, in particular for the prophylaxis and treatment of various disorders. Specifically suggested have been their use for the treatment and prophylaxis of the circulation, thrombosis, cardiac infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, tumor disorders, osteolytic disorders, especially osteoporosis, angiogenesis and disorders resulting from angiogenesis, for example diabetic retinopathy of the eye, macular degeneration, myopia, ocular histoplasmosis, rheumatic arthritis, osteoarthritis, rubeotic glaucoma, and also ulcerative colitis, Crohn's disease, multiple sclerosis, psoriasis and restenosis following angioplasty.

Eye diseases resulting from angiogenesis are the leading cause of visual loss in America. While in case of the population of the age of over 65 visual loss is predominantly effected by age-related macular degeneration (AMD) in case of population of the age of less than 65 this is predominantly effected by diabetic retinopathy.

In Wall Street Journal from March 6 th, 2000 an overview about occurence and current therapies of AMD is given. According to this AMD currently afflicts some 12 million Americans. AMD progressively destroys the macula which is responsible for central vision and color vision. In some cases,

deterioration of central vision to fuzzy blur can be rapid occuring in weeks or months. Two forms of the disease exists called „atrophic" and „exudative". Although exudative AMD effects only 10% of the total AMD population, it accounts for 90% of all AMD-related blindness.

Until recently, the only treatment for exudative AMD consisted of directing a powerful laser beam at the harmful blood vessels to heat and coagulate them. However, only about 15% of patients with exudative AMD have been eligible for this laser surgery. Other therapies are currently in experimental phase. In one approach, called photodynamic therapy, a low-power laser is combined with injection of light-absorbing dye. Another therapy is a more surgical approach and is called „limited retinal translocation". In this therapy the leaky vessels are destroyed with a high-powered laser after separation and rotation of the retina from the outer wall of the eye.

US 5,766,591 discribes the use of RGD-containing $\alpha_v\beta_3$ antagonists for the treatment of patients in which neovascularisation in the retinal tissue occurs. More specifically the use of said antagonists for the treatment of patients with diabetic retinopathy, macular degeneration and neovasular glaucoma is suggested. However, no examples with regard to this indications are presented. Concerning to the route of administration only general information are given. Specifically intravenous, intraperitoneal, intramuscular, intracavital and transdermal application is mentioned. In all cases $\alpha_v\beta_3$ antagonists are preferred exhibiting selectivity for $\alpha_v\beta_3$ over other integrins such as $\alpha_v\beta_5$.

WO 97/06791 A1 discribes that $\alpha_v\beta_5$ antagonists can be used for inhibiting angiogenesis too. Likewise as suggested for $\alpha_v\beta_3$ antagonists in US 5,766,591 $\alpha_v\beta_5$ antagonists are suggested for the treatment of a patient with diabetic retinopathy, macular degeneration and neovasular glaucoma. With

regard to the route of administration intravenous, intraocular, intrasynovial, intramuscular, transdermal and oral application is specifically mentioned.

DESCIPTION OF THE INVENTION

It has been found that inhibitors of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin receptors have particularly useful pharmacological and physicochemical properties combined with good tolerability, as, in particular, they can be used for prophylaxis and treatment of diseases of the eye of a patient resulting from angiogenesis in the eye by injecting the inhibitor into the subTenon's space of the eye.

Accordingly, the invention is directed to a method for prophylaxis and/or treatment of diseases of the eye of a patient resulting from angiogenesis in the eye comprising injecting into the subTenon's space of the eye of the eye of said patient a composition comprising a therapeutically effective amount of an $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor sufficient to inhibit angiogenesis of the eye.

Injection into subTenon's space (subTenon's injection) means that the medicament is placed into the space between sclera and Tenon's capsule using an appropriate injection device. SubTenon's injection is generally known by the person skilled in the art, see, for example, Li HK et al., Ophthalmology, Vol. 107, No. 1, 41-46 (2000).

Advantageously subTenon's injection is performed using the following procedure: (a) prepping and draping the eye in the usual fashion, (b) placing a lid speculum in the eye, (c) making a (ca. 1-2 mm) incision posterior to the limbus midway between the superior and lateral rectus musculus through conjunctiva and Tenon's capsule down to bare sclera, (d) grasping the

margins of the incision with a forceps and inserting the injection cannula through the incision io the space between bare slera and both conjunctiva and Tenon's capsule, (e) slowly injecting the contents of the syringe, advancing the tip of the cannula very slowly posteriorly and laterally taking care not to tear the capsule or conjunctiva or nearby blood vessels, (f) slowly retracting and finally removing the cannula from the globe after applying a cotton tipped applicator to the injection site just prior to extracting the cannula and, finally, (g) applying an antibiotic to the injection site.

A therapeutically effective amount is an amount of inhibitor sufficient to produce a measureable inhibition of angiogenesis in the tissue of the eye when injected into the subTenon's space. In general, this is the case when the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is used in an amount from about 0.5 µg to about 5 mg.

The method of invention is especially usable for prophylaxis and/or treatment of diabetic retinopathy, macular degeneration, myopia and histoplasmosis.

In a preferred embodiment of the invention polypeptides containing the amino acid sequence RGD are used as $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors in the method for prophylaxis and/or treatment of eye diseases. As mentioned above, RGD is the peptide sequence Arg-Gly-Asp (arginine-glycine-aspartic acid) occuring in natural ligands of integrins like fibronectin or vitronectin. Solvable RGD containing linear or cyclic peptides are able to inhibit interactions of this integrins with their corresponding natural ligands.

The abbreviations for the amino acid residues used hereinafter are shown in the following table:

Ala	A	alanine
Arg	R	arginine
Asp	D	aspartic acid
D-homoPhe		D-homo-phenylalanine
D-Nal		D-3-(2-naphthyl)alanine
D-Phe		D-phenylalanine
D-Phg		D-phenylglycine
D-Trp		D-tryptophan
D-Tyr		D-tyrosine
Gly	G	glycine
4-Hal-Phe		4-halo-phenylalanine
homoPhe		homo-phenylalanine
Ile	I	isoleucine
Leu	L	leucine
Nal		3-(2-naphthyl)alanine
Nle		norleucine
Phe	F	phenylalanine
Phg		phenylglycine
Trp	W	tryptophan
Tyr	Y	tyrosine
Val	V	valine.

Particularly preferred as $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors to be used in the method for prophylaxis and/or treatment of eye diseases are compounds of formula I

cyclo-(Arg-Gly-Asp-D-$(A)_n$E) I,

in which

D		is D-Phe, Phe, D-Trp, Trp, D-Tyr, Tyr, D-homoPhe, homoPhe, D-Nal, Nal, D-Phg, Phg or 4-Hal-Phe (D or L form), in which Hal is F, Cl, Br, I,
E		is Val, Gly, Ala, Leu, Ile or Nle,
A		is alkyl having 1-18 carbon atoms and
n		is 0 or 1

and also their physiologically acceptable salts.

In formula I alkyl is preferably methyl,ethyl, isopropyl, n-butyl, sec-butyl or tert-butyl.

More particular preferred polypeptides are used as $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors in the method of the invention that can be expressed by the subformula Ia, which otherwise corresponds to the formula I but in which

D is D-Phe and
E is Gly, Ala, Val, Leu, Ile or Nle.

Furthermore, particular preference is given to the use of all physiologically compatible salts of the compounds which come under the subformula Ia.

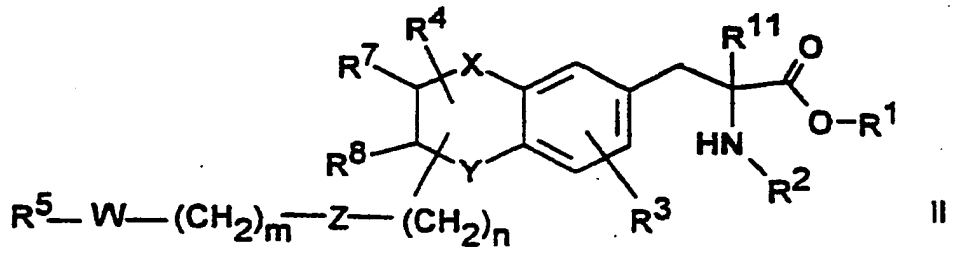
Most preferred as active compound in said method are cyclo-(Arg-Gly-Asp-DPhe-Val) and cyclo-(Arg-Gly-Asp-DPhe-NMeVal).

This RGD-containing peptides described by formula I as well as the peptides specifically mentioned hereinbefore are disclosed in EP 0 770 622 A2, the disclosure of which is hereby incorporated to the present application by reference. Accordingly, the meaning of the substituents of formula I resp.

subformula Ia are the same as defined for the substituents of subformula Ia resp. subformula Ib as disclosed on page 5, line 24 to line 32 resp. page 5, line 33 to line 41 in EP 0 770 662 A2.

It has been found that inhibitors of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin receptors which are no polypeptides and do not contain the RGD sequence can also be used for prophylaxis and treatment of diseases of the eye of a patient resulting from angiogenesis in the eye by injecting the inhibitor into the subTenon's space of the eye.

Therefore, in one further preferred embodiment of the method of invention the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors to be used in the method for prophylaxis or treatment of eye diseases are compounds of formula II



II

wherein

R^1	is H, alkyl having 1-6 C atoms or benzyl,
R^2	is R^{10}, CO-R^{10}, $COOR^6$, $COOR^{10}$, SO_2R^6 or SO_2R^{10},
R^3	is H, Hal, OA, NHR^{10}, $N(R^{10})_2$, -NH-acyl, -O-acyl, CN, NO_2, OR^{10}, SR^{10}, R^2 or $CONHR^{10}$,
R^4	is H, =O, =S, C_1-C_6-alkyl or acyl,
R^5	is NH_2, H_2N-C(=NH) or H_2N-(C=NH)-NH, where the primary amino groups can also be provided with conventional amino protective groups or can be mono-, di- or trisubstituted by R^{10},

		$CO\text{-}R^{10}$, $COOR^{10}$ or SO_2R^{10},or R^6,
	R^7, R^8	are each independently of one another absent or H,
	R^7 and R^8	together are also a bond,
	X, Y	are each independently of one another =N-, -N-, O, S, $-CH_2-$ or =C-, with the proviso that at least one of the two definitions X, Y is =N-, -N-, O or S,
	W, Z	are each independently of one another absent, O, S, NR^1, C(=O), CONH, NHCO, C(=S)NH, NHC(=S), C(=S), SO_2NH, $NHSO_2$ or CA=CA',
	R^6	is a mono- or binuclear heterocycle which has 1 to 4 N, O and/or S atoms and can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	R^9	is H, Hal, OA, NHA, NAA', NHacyl, Oacyl, CN, NO_2, SA, SOA, SO_2A, SO_2Ar or SO_3H,
	R^{10}	is H, A, Ar or aralkyl having 7-14 C atoms,
	R^{11}	is H or alkyl having 1-6 C atoms,
	A, A'	are each independently of one another H or unsubstituted or mono-, di- or tri-R^9-substituted alkyl or cycloalkyl, each of which has 1-15 C atoms and in which one, two or three methylene groups can be replaced by N, O and/or S,
	Ar	is unsubstituted or mono-, di- or tri-A- and/or R^9-substituted mono- or binuclear aromatic ring system having 0, 1, 2, 3 or 4 N, O and/or S atoms,
	Hal	is F, Cl, Br or I and
	m, n	are each independently of one another 0, 1, 2, 3 or 4,

and the physiologically acceptable salts thereof.

Particularly preferred $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors are used in the method of invention that can be expressed by the subformulae IIa to IIg, which otherwise corresponds to the formula II but in which

in IIa)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is H_2N-C(=NH) or H_2N-C(=NH)-NH,
	W, Z	are each independently of one another absent, C(=O), NH, CONH or NHCO,
	X	is -NH-, O or -CH_2-,
	Y	is NH or O,
	R^{10}	is H, A or benzyl,
	R^{11}	is H,
	A	is unsubstituted alkyl or cycloalkyl with 1-15 C atoms and
	m, n	are each independently of one another 0, 1 or 2;
in IIb)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is R^6,
	W, Z	are each independently of one another absent, C(=O), NH, CONH or NHCO,
	X	is -NH-, O or -CH_2-,
	Y	is NH or O,
	R^6	is a mono- or binuclear heterocycle which has 1-4 N, O and/or S atoms and which can be

unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,

R^{10} is H, A or benzyl,

R^{11} is H,

A is unsubstituted alkyl or cycloalkyl with 1-15 C atoms and

m, n are each independently of one another 0, 1 or 2;

in IIc)

R^1 is H or alkyl with 1-6 C atoms,

R^2 is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},

R^3 is H,

R^4 is H or =O,

R^5 is H_2N-C(=NH) or H_2N-C(=NH)-NH,

W, Z are each independently of one another absent, C(=O), NH, CONH or NHCO,

X is -NH-, O or $-CH_2-$,

Y is NH or O,

A is alkyl with 1-6 C atoms,

R^{10} is H, alkyl with 1-6 C atoms, camphor-10-yl or benzyl,

R^{11} is H,

m, n are each independently of one another 0, 1 or 2;

in IId)

R^1 is H or alkyl with 1-6 C atoms,

R^2 is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},

R^3 is H,

R^4 is H or =O,

R^5 is R^6,

W, Z are each independently of one another

			absent, C(=O), NH, CONH or NHCO,
		X	is =NH-, O or -CH_2-,
		Y	is NH or O,
		R^6	is a mono- or binuclear heterocycle which has 1-4 N, O and/or S atoms and which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
		R^{10}	is H, alkyl with 1-4 C atoms, camphor-10-yl or benzyl,
		R^{11}	is H,
		A	is unsubstituted alkyl with 1-6 C atoms and
		m, n	are each independently of one another 0, 1 or 2;
	in IIe)	R^1	is H or alkyl with 1-6 C atoms,
		R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
		R^3	is H,
		R^4	is H or =O,
		R^5	is R^6,
		W, Z	are each independently of one another absent, C(=O), NH, CONH or NHCO,
		X	is -NH-, O or -CH_2-,
		Y	is NH or O,
		R^6	is 1H-imidazol-2-yl, thiazol-2-yl, 1H-benzimidazol-2-yl, 2H-pyrazol-2-yl, 1H-tetrazol-5-yl, 2-imino-imidazolidin-4-on-5-yl, 1-A-1,5-dihydro-imidazol-4-on-2-yl, pyrimidin-2-yl or 1,4,5,6-tetrahydro-pyrimidin-2-yl,
		R^{10}	is H, alkyl with 1-4 C atoms, camphor-10-yl or benzyl,

		R^{11}	is H,
		A	is unsubstituted alkyl with 1-6 C atoms and
		m, n	are each independently of one another 0, 1 or 2;
	in IIf)	R^1	is H or alkyl with 1-6 C atoms,
		R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
		R^3	is H,
		R^4	is H or =O,
		R^5	is H_2N-C(=NH) or H_2N-C(=NH)-NH,
		W, Z	are each independently of one another absent, C(=O), NH, CONH or NHCO,
		X	is -NH-, O or $-CH_2-$,
		Y	is NH or O,
		R^{10}	is Ar,
		R^{11}	is H,
		A	is unsubstituted alkyl or cycloalkyl with 1-15 C atoms and
		m, n	are each independently of one another 0, 1 or 2;
	in IIg)	R^1	is H or alkyl with 1-6 C atoms,
		R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
		R^3	is H,
		R^4	is H or =O,
		R^5	is R^6,
		W, Z	are each independently of one another absent, C(=O), NH, CONH or NHCO,
		X	is -NH-, O or $-CH_2-$,
		Y	is NH or O,
		R^6	is a mono- or binuclear heterocycle which has 1-4 N, O and/or S atoms and which can be

		unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	R^{10}	is Ar,
	R^{11}	is H,
	A	is unsubstituted alkyl or cycloalkyl with 1-15 C. atoms and
	m, n	are each independently of one another 0, 1 or 2.

The compounds of formula II and subformulae IIa to IIg have been disclosed in DE 197 05 450 A1, the whole disclosure of which is hereby incorporated to the present application by reference. Accordingly, the substituents of formula II resp. subformulae IIa to IIg have the same meaning as defined for the substituents of formula I resp. subformulae Ia to Ig as disclosed on page 2, lines 3 to 43 resp. page 5, line 58 to page 7, line 30 of DE 197 05 450 A1. The definitions for the substituents are given on page 4, line 35 to page 5, line 56 of DE 197 05 450 A1.

More particularly preferred one of the following $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors is used in the method of the present invention:

(2S)-2-[(R)-camphor-10-sulfonamido]-3-{3,4-dihydro-2-(3-guanidino-propyl)-(2R)-2H-1,4-benzoxazin-3-on-6-yl}propionic acid;

(2S)-2-benzyloxycarboxamido-3-(2-guanidinomethyl-1,4-benzodioxan-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-[3,4-dihydro-2-(2-guanidino-2-oxoethyl)-2H-1,4-benzoxazin-3-on-6-yl]propionic acid;

(2S)-2-benzyloxycarboxamido-3-(2-guanidinoacet-amidomethyl-1,4-benzodioxan-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-{3,4-dihydro-2-[N-(2-imidazolyl)-

carbamoylmethyl]-2H-1,4-benzox-azin-3-on-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-{3,4-dihydro-2-[N-(2-benzimidazolyl)-carbamoylmethyl]-2H-1,4-benzoxazin-3-on-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-{3,4-dihydro-2-[2-(2-imino-4-oxoimidazolidin-5-yl)ethyl]-2H-1,4-benzoxazin-3-on-6-yl}propionic acid;

(2S)-2-(2,2-dimethylpropyloxycarboxamido)-3-{3,4-dihydro-2-[N-(2-imidazolyl)carbamoylethyl]-(2S)-2H-1,4-benzoxazin-3-on-6-yl}propionic acid;

(2S)-2-[(R)-camphorsulfonamido]-3-{3,4-dihydro-2-[N-(2-benzimidazolyl)carbamoylmethyl]-2H-1,4-benzoxazin-3-on-6-yl)propionic acid

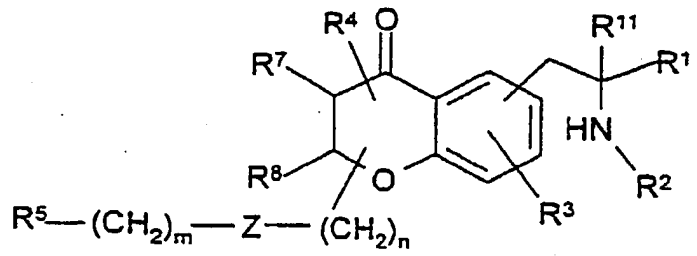
and their physiologically acceptable salts.

Most preferred are

(2S)-2-(2,2-dimethylpropyloxycarboxamido)-3-{3,4-dihydro-2-[N-(2-imidazolyl)carbamoyl-ethyl]-(2S)-2H-1,4-benzoxazin-3-on-6-yl}propionic acid and

(2S)-2-[(R)-camphorsulfonamido]-3-{3,4-dihydro-2-[N-(2-benzimidazolyl)-carbamoylmethyl]-2H-1,4-benzoxazin-3-on-6-yl)propionic acid:

In one further preferred embodiment of the method of invention the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors to be used in the method for prophylaxis or treatment of eye diseases are compounds of formula III



III

in which

R^1	is CH_2OR^{10}, $COOR^{10}$, $CONHR^{10}$ or $CON(R^{12})_2$,
R^2	is R^{10}, CO-R^{10}, CO-R^6, $COOR^6$, $COOR^{10}$, SO_2R^6, SO_2R^{10}, $CONHR^6$, $CON(R^6)_2$, $CONHR^{10}$ or $CON(R^{12})_2$,
R^3	is H, Hal, NHR^{10}, $N(R^{12})_2$, NH-acyl, -O-acyl, CN, NO_2, OR^{10}, SR^{10}, SO_2R^{10}, SO_3R^{10}, $COOR^{10}$, $CONHR^6$, $CON(R^6)_2$, $CONHR^{10}$ or $CON(R^{12})_2$,
R^4	is H, A, Ar or aralkylene having 7-14 C atoms,
R^5	is NH_2, H_2N-C(=NH) or H_2N-(C=NH)-NH, where the primary amino groups can also be provided with conventional amino protective groups, or can be mono- di- or trisubstituted by R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10}, or R^6-NH-,
R^6	is a mono- or binuclear heterocycle having 1 to 4 N, O and/or S atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
R^7, R^8	in each case independently of one another is absent or is H,
R^7 and R^8	together are also a bond,
Z	is absent, O, S, NH, NR^1, C(=O), CONH, NHCO, C(=S)NH, NHC(=S), C(=S), SO_2NH, $NHSO_2$ or CA=CA',
R^9	is H, Hal, OR^{11}, NH_2, NHR^{12}, $N(R^{12})_2$, NHAcyl, OAcyl, CN, NO_2, SR^{11}, SOR^{12}, SO_2R^{12} or SO_3H,
R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms,

R^{11}	is H or alkyl with 1-6 C atoms,	
R^{12}	is alkyl having 1-6 C atoms,	
A	is H or alkyl having 1-15 C atoms or cycloalkyl having 3-15 C atoms, which is unsubstituted or is mono-, di- or trisubstituted by R^9 and in which one, two or three methylene groups can also be replaced by N, O and/or S,	
Ar	is a mono- or binuclear aromatic ring system having 0, 1, 2, 3 or 4 N, O and/or S atoms, which is unsubstituted or mono-, di- or trisubstituted by A and/or R^9,	
Hal	is F, Cl, Br or I,	
m, n	in each case independently of one another are 0, 1, 2, 3 or 4,	

and their physiologically acceptable salts and solvates.

In this embodiment of the method of the present invention particularly preferred $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors are used that can be expressed by the subformulae IIIa to IIIn, which otherwise correspond to formula III but in which

in IIIa)	R^3	is H;	
in IIIb)	R^3	is H and	
	R^2	is $COOR^{10}$ or SO_2R^{10};	
in IIIc)	R^3	is H,	
	R^2	is $COOR^{10}$ or SO_2R^{10} and	
	R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms;	
in IIId)	m	is 0;	

	in IIIe)	m	is 0 and
		R^3	is H;
	in IIIf)	R^3	is H,
		R^2	is $COOR^{10}$ or SO_2R^{10} and
		m	is 0;
	in IIIg)	R^3	is H,
		R^2	is $COOR^{10}$ or SO_2R^{10} and
		R^{10}	is H, A, Ar or aralkylene with 7-14 C atoms and
		m	is 0;
	in IIIh)	R^3	is H,
		R^2	is $COOR^{10}$ or SO_2R^{10} and
		R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms and
		A	is H or unsubstituted alkyl having 1-15 C atoms or cycloalkyl having 3-15 C atoms;
		Ar	is phenyl or naphthyl and
		m	is 0;
	in IIIi)	R^6	is a mono- or binuclear heterocycle having 1 to 4 N atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	in IIIj)	R^3	is H,
		R^2	is $COOR^{10}$ or SO_2R^{10} and
		R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms and
		m	is 0;

		R^6	is a mono- or binuclear heterocycle having 1 to 4 N atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O;
	in IIIk)	Z	is absent;
	in IIIl)	Z	is absent and
		R^3	is H;
	in IIIm)	Z	is absent,
		R^3	is H and
		R^2	is $COOR^{10}$ or SO_2R^{10};
	in IIIn)	Z	is absent,
		R^3	is H,
		R^4	is H,
		R^2	is $COOR^{10}$ or SO_2R^{10};
		R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms,
		R^6	is a mono- or binuclear heterocycle having 1 to 4 N atoms, which can be unsubstituted or mono-, or risubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
		A	is H or unsubstituted alkyl having 1-6 C atoms,
		Ar	is phenyl or naphthyl and
		m	is 0.

The compounds of formula III and subformulae IIIa to IIIn have been disclosed in WO 00/26212 A1, the whole disclosure of which is incorporated to the present application by reference. Accordingly, the substituents of

formula III resp. subformulae IIIa to IIIn have the same meaning as defined for the substituents of formula I resp. subformulae Ia to In as disclosed on page 1, line 5 to page 2, line 31 resp. page 13, line 20 to page 15, line 6 of WO 00/26212 A1. The definitions for the substituents are given on page 8, line 18 to page 13, line 10 of WO 00/26212 A1.

More particularly preferred one of the following $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors is used in this embodiment of the method of the present invention:

(2S)-3-[2-(3-aminopropyl)-4-oxo-4*H*-chromen-6-yl]-2-(2,2-dimethylpropoxycarboxamido)-propionic acid;

(2S)-3-{2-[3-(1*H*-imidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(1*H*-imidazol-2-ylamino)propyl]-4-oxochroman-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(pyridin-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(1*H*-benzimidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(1H-imidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-butylsulfonamidopropionic acid;

(2S)-3-{2-[3-(pyridin-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,4,6-trimethylphenyl)sulfonamidopropionic acid

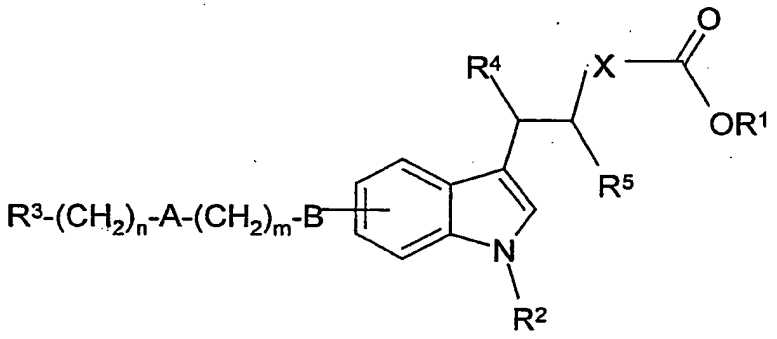
or their physiologically acceptable salts and solvates.

Most preferred are

(2S)-3-{2-[3-(1H-imidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-butylsulfonamidopropionic acid and

(2S)-3-{2-[3-(pyridin-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,4,6-trimethylphenyl)sulfonamidopropionic acid.

In one further preferred embodiment of the method of invention the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors to be used in the method for prophylaxis or treatment of eye diseases are compounds of formula IV



IV

wherein

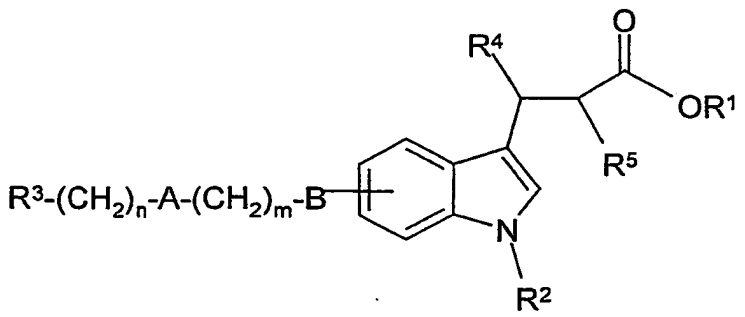
A and B		are each independently of one another O, S, NH, NR^7, CO, CONH, NHCO or directly bond,
X		is alkylene having 1-2 C atoms, which is unsubstituted or monosubstituted by R^4 or R^5 or a direct bond,
R^1		is H, Z or $-(CH_2)_o$-Ar,
R^2		is H, R^7 or -C(O)Z,
R^3		is NHR^6, $-NR^6$-C(=NR^6)-NHR^6, -C(=NR^6)-NHR^6, $-NR^6$-C(=NR^9)-NHR^6, -C(=NR^9)-NHR^6 or Het^1,
R^4 or R^5		are each indipendently of one another H, oxo, R^7, $-(CH_2)_o$-Ar, -C(O)-$(CH_2)_o$-Ar, -C(O)-$(CH_2)_o$-R^7, -C(O)-$(CH_2)_o$-Het, Het,
NHR^6,		NHAr, NH-Het, OR^7, OAr, OR^6 or O-Het,
R^6		is H, -C(O)R^7, -C(O)-Ar, R^7, $COOR^7$, COO-$(CH_2)_o$-Ar, SO_2-Ar, SO_2R^7 or SO_2-Het,

R^7		is alkyl having 1 to 10 C atoms or cycloalkyl having 1 to 10 C atoms,
R^8		is Hal, NO_2, CN, Z, $-(CH_2)_o$-Ar, $COOR^1$, OR^1, CF_3, OCF_3,
SO_2R^1,		NHR^1, $N(R^1)_2$, NH-C(O)R^1, $NHCOOR^1$ or C(O)R^1,
R^9		is CN or NO_2,
Z		is alkyl having 1 to 6 C atoms,
Ar		is aryl, which is unsubstituted or substituted by R^8,
Hal		is F, Cl, Br or I,
Het		is saturated, partly of fully saturated mono- or bicyclic heterocyclic ring system having 5 to 10 atoms, which can contain 1 or 2 N atoms and/or 1 or 2 S or O atoms and wherein the heterocyclic ring system can be mono- or disubstituted by R^8,
Het^1		is a mono or bicyclic aromatic heterocyclic ring system having 1 to 4 N atoms, which can be unsubstituted or mono- or disubstituted by Hal, R^7, OR^7, CN, NHZ or NO_2,
n		is 0, 1 or 2
m		is 0, 1, 2, 3, 4, 5 or 6,
o		is 0, 1 or 2

as well as their physiologically acceptable salts and solvates.

In this embodiment of the method of invention particularly preferred $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitors are used that can be expressed by the subformulae IVa to IVi, which otherwise correspond to formula IV but in which

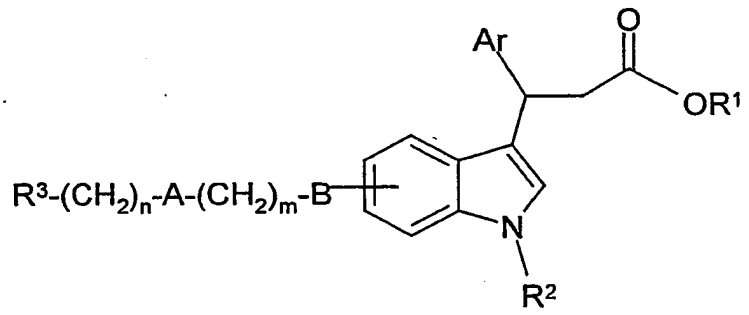
in IVa	X	is a direct bond



IVa

;

in IVb	X	is a direct bond,
	R^2	is H,
	R^5	is H and
	R^4	is Ar



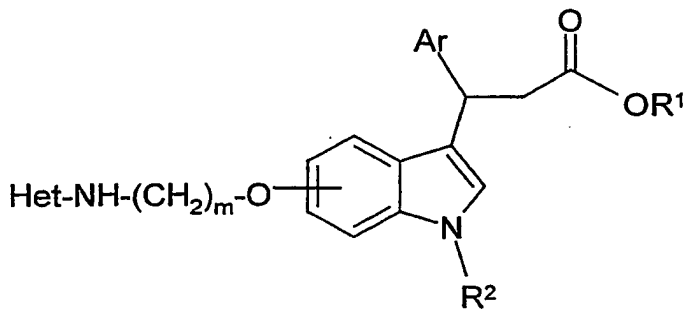
IVb

;

in IVc	X	is a direct bond,
	R^5	is H and
	R^4	is Ar or Het;

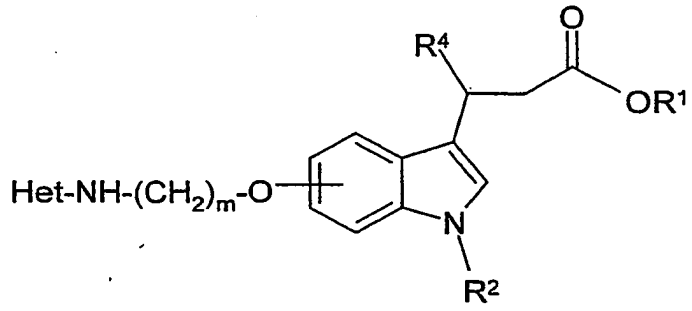
in IVd	X	is a direct bond,
	R^5	is H,
	B	is O,
	A	is NH,
	n	is 0,
	m	is 3 or 4,
	R^3	is Het and

R^4 is Ar



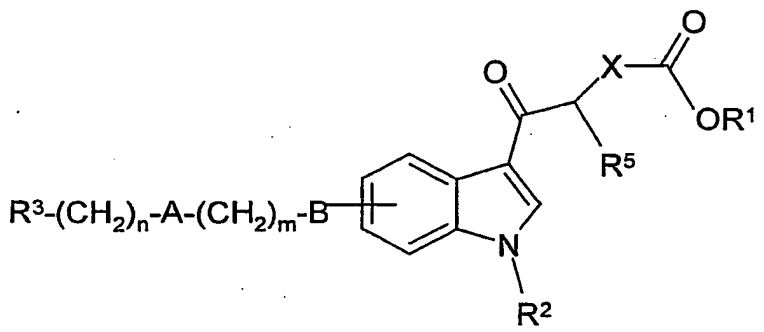
IVd ;

in IVe X is a direct bond,
R^5 is H,
B is O,
A is NH,
n is 0,
m is 3 or 4 and
R^3 is Het



IVe ;

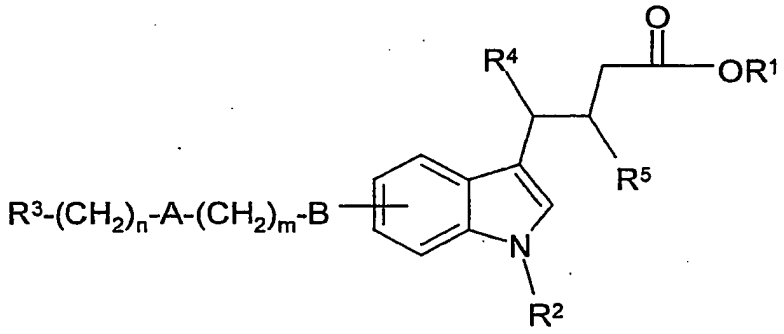
in IVf X is methylene, which is unsubstituted or substituted by Ar,
R^2 is H,
R^5 is H oder Ar and
R^4 is oxo



IVf

;

in IVg	X	is methylene,



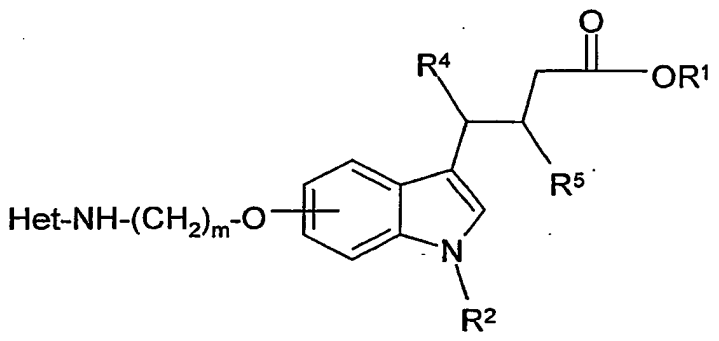
IVg

;

in IVh	X	is methylene,
	R^4	is H or Ar,
	R^5	is H or Ar and
	R^2	is H;

in IVi	X	is methylene,
	R^4	is H or Ar,
	R^5	is H or Ar,
	B	is O,
	A	is NH,
	n	is 0,
	m	is 3 or 4
	R^3	is Het and

R^2 is H



IVi

More particularly preferred the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor according to formula IV to be used in the method of the present invention is:

3-phenyl-3-{6-[3-(pyridine-2-ylamino)-propoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-{6-[4-(pyridine-2-ylamino)-butoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-{5-[4-(pyridine-2-ylamino)-butoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-{5-[3-(pyridine-2-ylamino)-propoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-[6-(pyridine-2-yl-amidocarboxymethoxy)-indole-3-yl]-propionic acid;

3-phenyl-3-[6-(benzimidazole-2-yl-amidocarboxymethoxy)-indole-3-yl]-propionic acid

3-phenyl-3-[6-(imidazole-2-yl-amidocarboxymethoxy)-indole-3-yl]-propionic acid or

3-Benzo[1,2,5]thiadiazol-5-yl-3-{6-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-1H-indol-3-yl}-propionic acid

as well as their physiologically acceptable salts and solvates.

Most preferred the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor according to formula IV to be used in the method of the present invention is

3-phenyl-3-{6-[3-(pyridine-2-ylamino)-propoxy]-1H-indole-3-yl}-propionic acid or

3-Benzo[1,2,5]thiadiazol-5-yl-3-{6-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-1H-indol-3-yl}-propionic acid.

This compounds as well as the compounds of formula IV and subformulae IVa to IVi are disclosed in copending german patent application no. 100 06 139.7, the whole disclosure of which is hereby incorporated to the present application by reference. Accordingly, the substituents of formula IV and subformulae IVa to IVi have the same meaning as defined for the substituents of formula I resp. subformulae Ia to Ii as disclosed on page 1, line 3 to page 2, line 13 resp. page 17, line 4 to page 20, line 9 of german patent application no. 100 06 139.7. The definitions for the substituents are given on page 9, line 6 to page 16, line 28 of german patent application no. 100 06 139.7.

The particular suitability of the compounds as described hereinbefore for using in the method of treatment of eye diseases was experimentally confirmed for some representative compounds.

It is a further object of the invention to provide a composition suitable for the method for prophylaxis and treatment of diseases of the eye of a patient resulting from angiogenesis comprising injecting into the subTenon's space of the eye of said patient a composition comprising a therapeutically effective amount of an $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor sufficient to inhibit angiogenesis of the eye.

The formulation used for administration of the compound into the subTenon's space of the eye can be any form suitable for application into the subTenon's space by injection through a cannula with small diameter suitable for injection into the subTenon's space. Examples for injectable application forms are solutions, suspensions or colloidal suspensions.

Compositions usable for injection into the subTenon's space contain a physiologically tolerable carrier together with the relevant agent as described herein, dissolved or dispersed therein as an active ingredient. As used herein, the term "pharmaceutically acceptable" refers to compositions, carriers, diluents and reagents which represent materials that are capable of administration into the subTenon's space of a mammal without the production of undesirable physiological effects. The preparation of a injectable pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art and need not be limited based on formulation. The preparation can also be emulsified. The active ingredient can be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Suitable excipients are, for example, water, saline, sorbitol, glycerol or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and the like which enhance the effectiveness of the active ingredient. The composition can also contain viscosity enhancing agents like hyaluronic acid. The therapeutic composition of the present invention can include pharmaceutically acceptable salts of the components therein. Pharmaceutically acceptable salts include the acid addition salts that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, tartaric, mandelic and the like. Salts formed with the free carboxyl groups can also

be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and the like. Particularly preferred is the HCl salt.

Physiologically tolerable carriers are well known in the art. Exemplary of liquid carriers are sterile aqueous solutions that contain no materials in addition to the active ingredients and water, or contain a buffer such as sodium phosphate at physiological pH value, physiological saline or both, such as phosphate-buffered saline. Still further, aqueous carriers can contain more than one buffer salt, as well as salts such as sodium and potassium chlorides, sorbitol and other solutes.

Depending from the application form the active compound liberates in an immediate or a sustained release manner. A sustained release formulation is preferred because the injection frequency can be reduced.

One possibility to achieve sustained release kinetics is embedding or encapsulating the active compound into nanoparticles. Nanoparticles can be administrated as powder, as powder mixture with added excipients or as suspensions. Colloidal suspensions of nanoparticles are preferred because they can easily be administrated through a cannula with small diameter.

Nanoparticles are particles with a diameter from about 5 nm to up to about 1000 nm. The term „nanoparticles" as it is used hereinafter refers to particles formed by a polymeric matrix in which the active compound is dispersed, also known as „nanospheres", and also refers to nanoparticles which are composed of a core containing the active compound which is surrounded by a polymeric membrane, also known as „nanocapsules". For administration into the subTenon's space of the eye nanoparticles are preferred having a

diameter from about 50 nm to about 500 nm, in particular from about 100 nm to about 200 nm.

Nanoparticles can be prepared by in situ polymerization of dispersed monomers or by using preformed polymers. Since polymers prepared in situ are often not biodegradable and/or contain toxicological serious byproducts nanoparticles from preformed polymers are preferred. Nanoparticles from preformed polymers can be prepared by different techniques, i.e. by emulsion evaporation, solvent displacement, salting-out and by emulsification diffusion.

Emulsion evaporation is the classical technique for preparation of nanoparticles from preformed polymers. According to this technique, the polymer and the active compounds are dissolved in a water-immiscible organic solvent, which is emulsified in an aqueous solution. The crude emulsion is then exposed to a high-energy source such as ultrasonic devices or passed through high pressure homogenizers or microfluidizers to reduce the particle size. Subsequently the organic solvent is removed by heat and/or vacuum resulting in formation of the nanoparticles with a diameter of about 100 nm to about 300 nm. Usually, methylene chloride and chloroform are used as organic solvent because of their water insolubility, good solubilizing properties, easy emulsification and high volatility. These solvents are, however, critical in view of their physiological tolerability. Moreover, the high shear force needed for particle size reduction can lead to damage of polymer and/or the active compound.

The solvent displacement process was firstly described in EP 0 274 961 A1. In this process the active compound and the polymer are dissolved in an organic solvent which is miscible with water in all proportions. This solution is introduced in an aqueous solution containing a stabilizer under gentle

agitation resulting in spontaneous formation of nanoparticles. Examples for suitable organic solvents and stabilizer are acetone or ethanol resp. polyvinyl alcohol. Advantageously chlorinated solvents and shear stress can be avoided. The mechanism of formation of nanoparticles has been explained by interfacial turbulence generated during solvent displacement (Fessi H. et al., Int. J. Pharm. 55 (1989) R1-R4). Recently, a solvent displacement technique was disclosed by WO 97/03657 A1, in which the organic solvent containing the active compound and the polymer is introduced into the aqueous solution without agitation.

The salting-out technique was firstly described in WO 88/08011 A1. In this technique a solution of a water-insoluble polymer and an active compound in a water-soluble organic solvent, especially acetone, is mixed with a concentrated aqueous viscous solution or gel containing a colloidal stabilizer and a salting-out agent. To the resulting oil-in-water emulsion water is added in a quantity sufficient to diffuse into the aqueous phase and to induce rapid diffusion of the organic solvent into the aqueous phase leading to interfaciale turbulence and formation of nanoparticles. The organic solvent and the salting-out agent remaining in the suspension of nanoparticles are subsequently eliminated by repeated washing with water. Alternatively, the solvent and salting-out agent can be eliminated by cross-flow filtration.

In emulsification-diffusion process the polymer is dissolved in a water-saturated partially water-soluble organic solvent. This solution is mixed with an aqueous solution containing a stabilizer resulting in an oil-in-water emulsion. To this emulsion water is added causing the solvent to diffuse into the aqueous external phase accompanied with formation of nanoparticles. During particle formation each emulsion droplet leads to several nanoparticle. As this phenomenon cannot be fully explained by convection effect caused by interfacial turbulence, it has been proposed that diffusion of

organic solvent from the droplets of the crude emulsion carries molecules of active compound and polymer phase into the aqueous phase resulting in supersaturated local regions, from which the polymer aggregates in the form of nanoparticles (Quintanar-Guerrero D. et al. Colloid. Polym. Sci. 275 (1997) 640-647). Advantageously, pharmaceutically acceptable solvents like propylene carbonate or ethyl acetate can be used as organic solvents.

With the methods described above nanoparticles can be formed with various types of polymers. For use in the method of the present invention, which involves injection of the formulation into the subTenon's space of the eye, nanoparticles made from biocompatible polymers are preferred. The term „biocompatible" refers to material which, after introducing in a biological environment, have no serious effects to the biological environment. From biocompatible polymers those polymers are especially preferred which are also biodegradable. The term „biodegradable" refers to material which, after introducing in a biological environment, is enzymatically or chemically degraded into smaller molecules which can be eliminated subsequently.

Biodegradable polymers are well known by the person skilled in the art. Examples are polyesters from hydroxycarboxylic acids such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), polycaprolactone (PCL), copolymers of lactic acid and glycolic acid (PLGA), copolymers of lactic acid and caprolactone, polyepsilon caprolactone, polyhyroxy butyric acid and poly(ortho)esters, polyurethanes, polyanhydrides, polyacetals, polydihydropyrans, polycyanoacrylates, natural polymers such as alginate and other polysaccharides including dextran and cellulose, collagen and albumin.

Liposomes are a further drug delivery system which is easily injectable. Accordingly, in the method of invention the active compounds can also be

administered into the subTenon's space of the eye in the form of a liposome delivery system. Liposomes are well-known by a person skilled in the art. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine of phosphatidylcholines. Liposomes being usable for the method of invention encompass all types of liposomes including, but not limited to, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles.

What claimed is:

1. A method for prophylaxis and/or treatment of diseases of the eye of a patient resulting from angiogenesis in the eye comprising injecting into the subTenon's space of the eye of said patient a composition comprising a therapeutically effective amount of an $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor sufficient to inhibit angiogenesis of the eye

2. A method of Claim 1 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a RGD-containing polypeptide

3. A method of Claim 2 wherein said polypeptide is a compound of formula I

cyclo-(Arg-Gly-Asp-D-$(A)_n$E) I,

in which

D is D-Phe, Phe, D-Trp, Trp, D-Tyr, Tyr, D-homoPhe, homoPhe, D-Nal, Nal, D-Phg, Phg or 4-Hal-Phe (D or L form),
E is Val, Gly, Ala, Leu, Ile or Nle and
A is alkyl having 1-18 carbon atoms,
n 0 or 1

and also their physiologically acceptable salts

4. A method of Claim 2 wherein said polypeptide is a compound as expressed by subformula Ia, which otherwise correspond to formula I but in which

D is D-Phe and

E is Gly, Ala, Val, Leu, Ile or Nle.

5. A method of Claim 2 wherein said polypeptide is cyclo-(Arg-Gly-Asp-DPhe-Val)

6. A method of Claim 2 wherein said polypeptide is cyclo-(Arg-Gly-Asp-DPhe-NMeVal)

7. A method of Claim 2 wherein said therapeutically efective amount is from about 0.5 µg to 5 mg

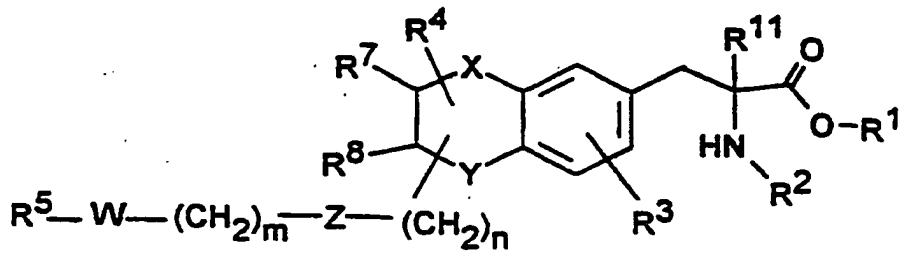
8. A method of Claim 2 wherein said eye disease is diabetic retinopathy

9. A method of Claim 2 wherein said eye disease is macular degeneration

10. A method of Claim 2 wherein said eye disease is myopia

11. A method of Claim 2 wherein said eye disease is ocular histoplasmosis

12. A method of Claim 1 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound of formula II



II

wherein

R^1		is H, alkyl having 1-6 C atoms or benzyl,
R^2		is R^{10}, CO-R^{10}, $COOR^6$, $COOR^{10}$, SO_2R^6 or SO_2R^{10},
R^3		is H, Hal, OA, NHR^{10}, $N(R^{10})_2$, -NH-acyl, -O-acyl, CN, NO_2, OR^{10}, SR^{10}, R^2 or $CONHR^{10}$,
R^4		is H, =O, =S, C_1-C_6-alkyl or acyl,
R^5		is NH_2, H_2N-C(=NH) or H_2N-(C=NH)-NH, where the primary amino groups can also be provided with conventional amino protective groups or can be mono-, di- or trisubstituted by R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},or R^6,
R^7, R^8		are each independently of one another absent or H,
R^7 and R^8		together are also a bond,
X, Y		are each independently of one another =N-, -N-, O, S, $-CH_2-$ or =C-, with the proviso that at least one of the two definitions X, Y is =N-, -N-, O or S,
W, Z		are each independently of one another absent, O, S, NR^1, C(=O), CONH, NHCO, C(=S)NH, NHC(=S), C(=S), SO_2NH, $NHSO_2$ or CA=CA',
R^6		is a mono- or binuclear heterocycle which has 1 to 4 N, O and/or S atoms and can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
R^9		is H, Hal, OA, NHA, NAA', NHacyl, Oacyl, CN, NO_2, SA, SOA, SO_2A, SO_2Ar or SO_3H,
R^{10}		is H, A, Ar or aralkyl having 7-14 C atoms,
R^{11}		is H or alkyl having 1-6 C atoms,

A, A' are each independently of one another H or unsubstituted or mono-, di- or tri-R^9-substituted alkyl or cycloalkyl, each of which has 1-15 C atoms and in which one, two or three methylene groups can be replaced by N, O and/or S,

Ar is unsubstituted or mono-, di- or tri-A- and/or R^9-substituted mono- or binuclear aromatic ring system having 0, 1, 2, 3 or 4 N, O and/or S atoms,

Hal is F, Cl, Br or I and

m, n are each independently of one another 0, 1, 2, 3 or 4,

or a the physiologically acceptable salts thereof

13. A method of Claim 12 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is selected from the group consisting of compounds of subformulae IIa to IIg, which otherwise correspond to formula II but in which

in IIa)

R^1 is H or alkyl with 1-6 C atoms,

R^2 is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},

R^3 is H,

R^4 is H or =O,

R^5 is H_2N-C(=NH) or H_2N-C(=NH)-NH,

W, Z are each independently of one another absent, C(=O), NH, CONH or NHCO,

X is -NH-, O or $-CH_2-$,

Y is NH or O,

R^{10} is H, A or benzyl,

R^{11} is H,

A is unsubstituted alkyl or cycloalkyl with 1-15 C

		atoms and
	m, n	are each independently of one another 0, 1 or 2;
in IIb)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is R^6,
	W, Z	are each independently of one another absent,
		C(=O), NH, CONH or NHCO,
	X	is -NH-, O or $-CH_2-$,
	Y	is NH or O,
	R^6	is a mono- or binuclear heterocycle which has 1-4 N, O and/or S atoms and which can be
		unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	R^{10}	is H, A or benzyl,
	R^{11}	is H,
	A	is unsubstituted alkyl or cycloalkyl with 1-15 C atoms and
	m, n	are each independently of one another 0, 1 or 2;
in IIc)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is H_2N-C(=NH) or H_2N-C(=NH)-NH,
	W, Z	are each independently of one another absent,
		C(=O), NH, CONH or NHCO,

	X	is -NH-, O or -CH_2-,
	Y	is NH or O,
	A	is alkyl with 1-6 C atoms,
	R^{10}	is H, alkyl with 1-6 C atoms, camphor-10-yl or benzyl,
	R^{11}	is H,
	m, n	are each independently of one another 0, 1 or 2;
in IId)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is R^6,
	W, Z	are each independently of one another absent, C(=O), NH, CONH or NHCO,
	X	is =NH-, O or -CH_2-,
	Y	is NH or O,
	R^6	is a mono- or binuclear heterocycle which has 1-4 N, O and/or S atoms and which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	R^{10}	is H, alkyl with 1-4 C atoms, camphor-10-yl or benzyl,
	R^{11}	is H,
	A	is unsubstituted alkyl with 1-6 C atoms and
	m, n	are each independently of one another 0, 1 or 2;
in IIe)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},

	R^3	is H,
	R^4	is H or =O,
	R^5	is R^6,
	W, Z	are each independently of one another absent,
		C(=O), NH, CONH or NHCO,
	X	is -NH-, O or $-CH_2-$,
	Y	is NH or O,
	R^6	is 1H-imidazol-2-yl, thiazol-2-yl, 1H-benzimidazol-2-yl, 2H-pyrazol-2-yl, 1H-tetrazol-5-yl, 2-imino-imidazolidin-4-on-5-yl, 1-A-1,5-dihydro-imidazol-4-on-2-yl, pyrimidin-2-yl or 1,4,5,6-tetrahydro-pyrimidin-2-yl,
	R^{10}	is H, alkyl with 1-4 C atoms, camphor-10-yl or benzyl,
	R^{11}	is H,
	A	is unsubstituted alkyl with 1-6 C atoms and
	m, n	are each independently of one another 0, 1 or 2;
in IIf)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is H_2N-C(=NH) or H_2N-C(=NH)-NH,
	W, Z	are each independently of one another
		absent, C(=O), NH, CONH or NHCO,
	X	is -NH-, O or $-CH_2-$,
	Y	is NH or O,
	R^{10}	is Ar,
	R^{11}	is H,
	A	is unsubstituted alkyl or cycloalkyl with 1-15 C

		atoms and
	m, n	are each independently of one another 0, 1 or 2;
in IIg)	R^1	is H or alkyl with 1-6 C atoms,
	R^2	is R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10},
	R^3	is H,
	R^4	is H or =O,
	R^5	is R^6,
	W, Z	are each independently of one another absent,
		C(=O), NH, CONH or NHCO,
	X	is -NH-, O or -CH_2-,
	Y	is NH or O,
	R^6	is a mono- or binuclear heterocycle which has 1-4 N, O and/or S atoms and which can be
		unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	R^{10}	is Ar,
	R^{11}	is H,
	A	is unsubstituted alkyl or cycloalkyl with 1-15 C. atoms and
	m, n	are each independently of one another 0, 1 or 2

14. A method according to Claim 12 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound selected from the group consisting of

(2S)-2-[(R)-camphor-10-sulfonamido]-3-{3,4-dihydro-2-(3-guanidinopropyl)-(2R)-2H-1,4-benzoxazin-3-on-6-yl}propionic acid;

(2S)-2-benzyloxycarboxamido-3-(2-guanidinomethyl-1,4-benzodioxan-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-[3,4-dihydro-2-(2-guanidino-2-oxoethyl)-2H-1,4-benzoxazin-3-on-6-yl]propionic acid;

(2S)-2-benzyloxycarboxamido-3-(2-guanidinoacet-amidomethyl-1,4-benzodioxan-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-{3,4-dihydro-2-[N-(2-imidazolyl)-carbamoylmethyl]-2H-1,4-benzox-azin-3-on-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-{3,4-dihydro-2-[N-(2-benzimidazolyl)carbamoylmethyl]-2H-1,4-benzoxazin-3-on-6-yl)propionic acid;

(2S)-2-tert-butyloxycarboxamido-3-{3,4-dihydro-2-[2-(2-imino-4-oxoimidazolidin-5-yl)ethyl]-2H-1,4-benzoxazin-3-on-6-yl}propionic acid;

(2S)-2-(2,2-dimethylpropyloxycarboxamido)-3-{3,4-dihydro-2-[N-(2-imidazolyl)carbamoylethyl]-(2S)-2H-1,4-benzoxazin-3-on-6-yl}propionic;

(2S)-2-[(R)-camphorsulfonamido]-3-{3,4-dihydro-2-[N-(2-benzimidazolyl)carbamoylmethyl]-2H-1,4-benzoxazin-3-on-6-yl)propionic acid

and their physiologically acceptable salts

15. A method according to Claim 12 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is

(2S)-2-(2,2-dimethylpropyloxycarboxamido)-3-{3,4-dihydro-2-[N-(2-imidazolyl)carbamoylethyl]-(2S)-2H-1,4-benzoxazin-3-on-6-yl}propionic acid or

(2S)-2-[(R)-camphorsulfonamido]-3-{3,4-dihydro-2-[N-(2-benzimidazolyl)carbamoylmethyl]-2H-1,4-benzoxazin-3-on-6-yl)propionic acid

16. A method of Claim 12 wherein said amount is from about 0.5 µg to 5 mg

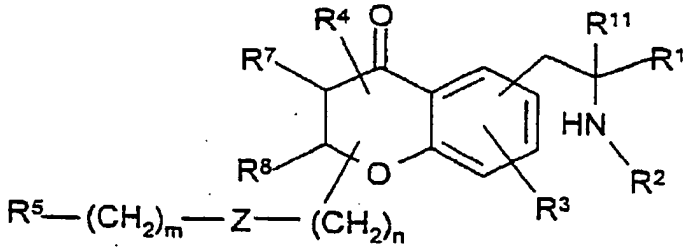
17. A method of Claim 12 wherein said eye disease is diabetic retinopathy

18. A method of Claim 12 wherein said eye disease is macular degeneration

19. A method of Claim 12 wherein said eye disease is myopia

20. A method of Claim 12 wherein said eye disease is ocular histoplasmosis

21. A method of Claim 1 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound of formula III



III

in which

R^1	is CH_2OR^{10}, $COOR^{10}$, $CONHR^{10}$ or $CON(R^{12})_2$,
R^2	is R^{10}, CO-R^{10}, CO-R^6, $COOR^6$, $COOR^{10}$, SO_2R^6, SO_2R^{10}, $CONHR^6$, $CON(R^6)_2$, $CONHR^{10}$ or $CON(R^{12})_2$,
R^3	is H, Hal, NHR^{10}, $N(R^{12})_2$, NH-acyl, -O-acyl, CN, NO_2, OR^{10}, SR^{10}, SO_2R^{10}, SO_3R^{10}, $COOR^{10}$, $CONHR^6$, $CON(R^6)_2$, $CONHR^{10}$ or $CON(R^{12})_2$,
R^4	is H, A, Ar or aralkylene having 7-14 C atoms,
R^5	is NH_2, H_2N-C(=NH) or H_2N-(C=NH)-NH, where the primary amino groups can also be provided with conventional amino protective groups, or can be mono- di- or trisubstituted by

		R^{10}, CO-R^{10}, $COOR^{10}$ or SO_2R^{10}, or R^6-NH-,
	R^6	is a mono- or binuclear heterocycle having 1 to 4 N, O and/or S atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
	R^7, R^8	in each case independently of one another is absent or is H,
	R^7 and R^8	together are also a bond,
	Z	is absent, O, S, NH, NR^1, C(=O), CONH, NHCO, C(=S)NH, NHC(=S), C(=S), SO_2NH, $NHSO_2$ or CA=CA',
	R^9	is H, Hal, OR^{11}, NH_2, NHR^{12}, $N(R^{12})_2$, NHAcyl, OAcyl, CN,
	NO_2,	SR^{11}, SOR^{12}, SO_2R^{12} or SO_3H,
	R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms,
	R^{11}	is H or alkyl with 1-6 C atoms,
	R^{12}	is alkyl having 1-6 C atoms,
	A	is H or alkyl having 1-15 C atoms or cycloalkyl having 3-15 C atoms, which is unsubstituted or is mono-, di- or trisubstituted by R^9 and in which one, two or three methylene groups can also be replaced by N, O and/or S,
	Ar	is a mono- or binuclear aromatic ring system having 0, 1, 2, 3 or 4 N, O and/or S atoms, which is unsubstituted or mono-, di- or trisubstituted by A and/or R^9,
	Hal	is F, Cl, Br or I,
	m, n	in each case independently of one another are 0, 1, 2, 3 or 4,

and their physiologically acceptable salts and solvates

22. A method of Claim 21 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is selected from the group consisting of compounds of subformulae IIIa to IIIn, which otherwise correspond to formula III but in which

in IIIa)	R^3	is H;	
in IIIb)	R^3	is H and	
	R^2	is $COOR^{10}$ or SO_2R^{10};	
in IIIc)	R^3	is H,	
	R^2	is $COOR^{10}$ or SO_2R^{10} and	
	R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms;	
in IIId)	m	is 0;	
in IIIe)	m	is 0 and	
	R^3	is H;	
in IIIf)	R^3	is H,	
	R^2	is $COOR^{10}$ or SO_2R^{10} and	
	m	is 0;	
in IIIg)	R^3	is H,	
	R^2	is $COOR^{10}$ or SO_2R^{10} and	
	R^{10}	is H, A, Ar or aralkylene with 7-14 C atoms and	
	m	is 0;	
in IIIh)	R^3	is H,	
	R^2	is $COOR^{10}$ or SO_2R^{10} and	
	R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms and	

		A	is H or unsubstituted alkyl having 1-15 C atoms or cycloalkyl having 3-15 C atoms,
		Ar	is phenyl or naphthyl and
		m	is 0;
	in IIIi)	R^6	is a mono- or binuclear heterocycle having 1 to 4 N atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O;
	in IIIj)	R^3	is H,
		R^2	is $COOR^{10}$ or SO_2R^{10} and
		R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms and
		m	is 0;
		R^6	is a mono- or binuclear heterocycle having 1 to 4 N atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O;
	in IIIk)	Z	is absent;
	in IIIl)	Z	is absent and
		R^3	is H;
	in IIIm)	Z	is absent,
		R^3	is H and
		R^2	is $COOR^{10}$ or SO_2R^{10};
	in IIIn)	Z	is absent,
		R^3	is H,

R^4	is H,
R^2	is $COOR^{10}$ or SO_2R^{10};
R^{10}	is H, A, Ar or aralkylene having 7-14 C atoms,
R^6	is a mono- or binuclear heterocycle having 1 to 4 N atoms, which can be unsubstituted or mono-, di- or trisubstituted by Hal, A, -CO-A, OH, CN, COOH, COOA, $CONH_2$, NO_2, =NH or =O,
A	is H or unsubstituted alkyl having 1-6 C atoms,
Ar	is phenyl or naphthyl and
m	is 0

23. A method according to Claim 21 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound selected from the group consisting of

(2S)-3-[2-(3-aminopropyl)-4-oxo-4*H*-chromen-6-yl]-2-(2,2-dimethylpropoxycarboxamido)-propionic acid;

(2S)-3-{2-[3-(1*H*-imidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(1*H*-imidazol-2-ylamino)propyl]-4-oxochroman-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(pyridin-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(1*H*-benzimidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,2-dimethylpropoxycarboxamido)propionic acid;

(2S)-3-{2-[3-(1H-imidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-butylsulfonamidopropionic acid

(2S)-3-{2-[3-(pyridin-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,4,6-trimethylphenyl)sulfonamidopropionic acid

and their physiologically acceptable salts and solvates

24. A method according to Claim 21 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound selected from the group consisting of

(2S)-3-{2-[3-(1H-imidazol-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-butylsulfonamidopropionic acid and

(2S)-3-{2-[3-(pyridin-2-ylamino)propyl]-4-oxo-4*H*-chromen-6-yl}-2-(2,4,6-trimethylphenyl)sulfonamidopropionic acid

25. A method of Claim 21 wherein said amount is from about 0.5 µg to 5 mg

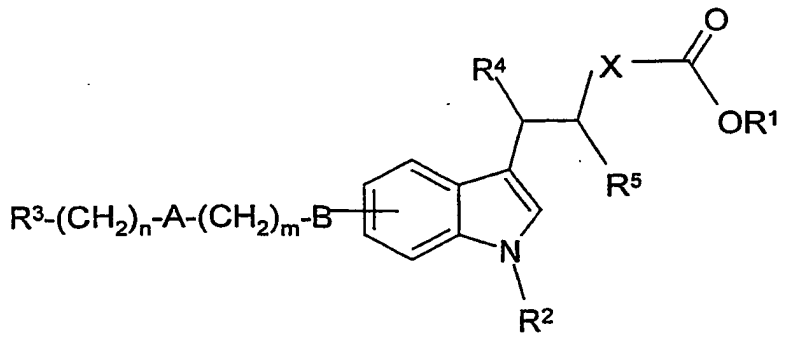
26. A method of Claim 21 wherein said eye disease is diabetic retinopathy

27. A method of Claim 21 wherein said eye disease is macular degeneration

28. A method of Claim 21 wherein said eye disease is myopia

29. A method of Claim 21 wherein said eye disease is ocular histoplasmosis

30. A method of Claim 1 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound of formula IV



IV

wherein

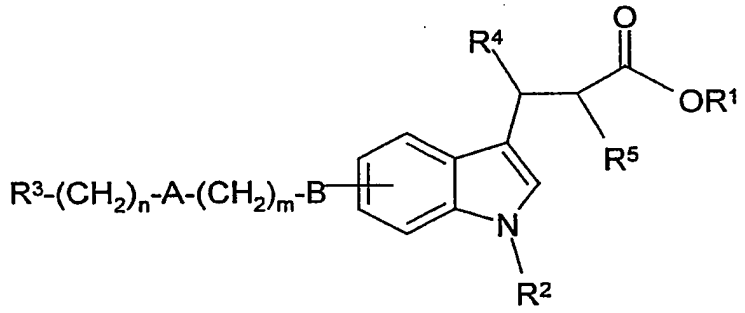
A and B	are each independently of one another O, S, NH, NR^7, CO, CONH, NHCO or directly bond,
X	is alkylene having 1-2 C atoms, which is unsubstituted or monosubstituted by R^4 or R^5 or a direct bond,
R^1	is H, Z or $-(CH_2)_o$-Ar,
R^2	is H, R^7 or -C(O)Z,
R^3	is NHR^6, $-NR^6-C(=NR^6)-NHR^6$, $-C(=NR^6)-NHR^6$, $-NR^6-C(=NR^9)-NHR^6$, $-C(=NR^9)-NHR^6$ or Het^1,
R^4 or R^5	are each indipendently of one another H, oxo, R^7, $-(CH_2)_o$-Ar, $-C(O)-(CH_2)_o$-Ar, $-C(O)-(CH_2)_o-R^7$, $-C(O)-(CH_2)_o$-Het, Het, NHR^6, NHAr, NH-Het, OR^7, OAr, OR^6 or O-Het,
R^6	is H, $-C(O)R^7$, -C(O)-Ar, R^7, $COOR^7$, $COO-(CH_2)_o$-Ar, SO_2-Ar, SO_2R^7 or SO_2-Het,
R^7	is alkyl having 1 to 10 C atoms or cycloalkyl having 1 to 10 C atoms,
R^8	is Hal, NO_2, CN, Z, $-(CH_2)_o$-Ar, $COOR^1$, OR^1, CF_3, OCF_3, SO_2R^1, NHR^1, $N(R^1)_2$, NH-C(O)R^1, $NHCOOR^1$ or C(O)R^1,
R^9	is CN or NO_2,
Z	is alkyl having 1 to 6 C atoms,
Ar	is aryl, which is unsubstituted or substituted by R^8,
Hal	is F, Cl, Br or I,
Het	is saturated, partly of fully saturated mono- or bicyclic heterocyclic ring system having 5 to 10 atoms, which
can	contain 1 or 2 N atoms and/or 1 or 2 S or O atoms and wherein the heterocyclic ring system can be mono or disubstituted by R^8,

Het^1		is a mono or bicyclic aromatic heterocyclic ring system having 1 to 4 N atoms, which can be unsubstituted or mono or disubstituted by Hal, R^7, OR^7, CN, NHZ or NO_2,
n		is 0, 1 or 2
m		is 0, 1, 2, 3, 4, 5 or 6,
o		is 0, 1 or 2

as well as their physiologically acceptable salts and solvates

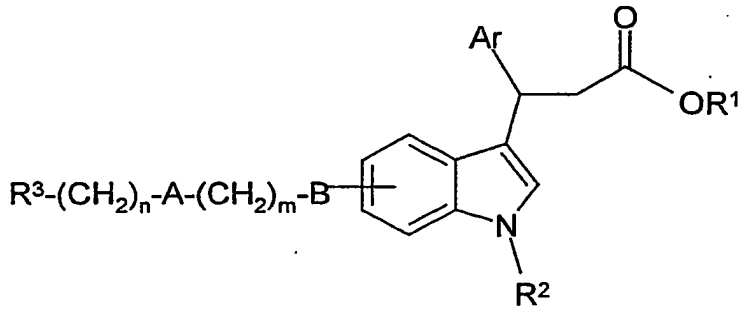
31. A method according to Claim 30 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is selected of the group consisting of compounds of subformulae IVa to IVi, which otherwise correspond to formula IV but in which

in IVa	X	is a direct bond



IVa ;

in IVb	X	is a direct bond,
	R^2	is H,
	R^5	is H and
	R^4	is Ar

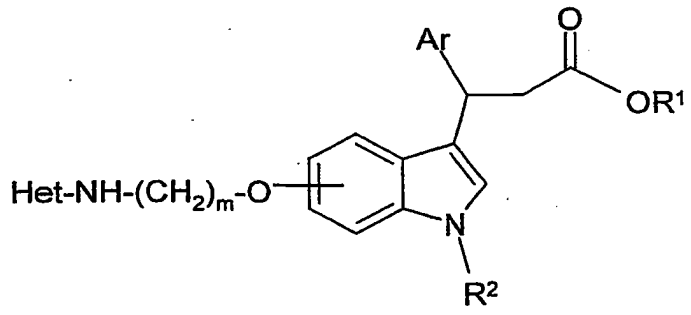


IVb

;

in IVc	X	is a direct bond,
	R^5	is H and
	R^4	is Ar or Het;

in IVd	X	is a direct bond,
	R^5	is H,
	B	is O,
	A	is NH,
	n	is 0,
	m	is 3 or 4,
	R^3	is Het and
	R^4	is Ar

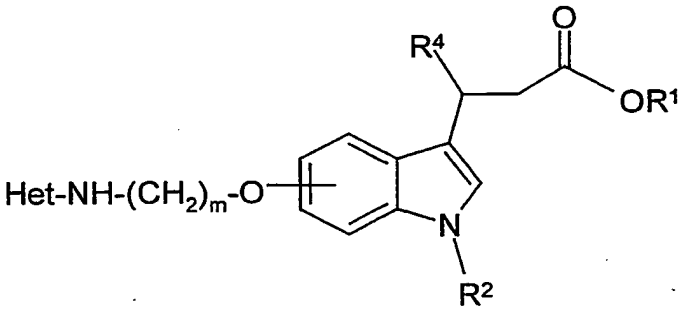


IVd

;

in IVe	X	is a direct bond,
	R^5	is H,
	B	is O,

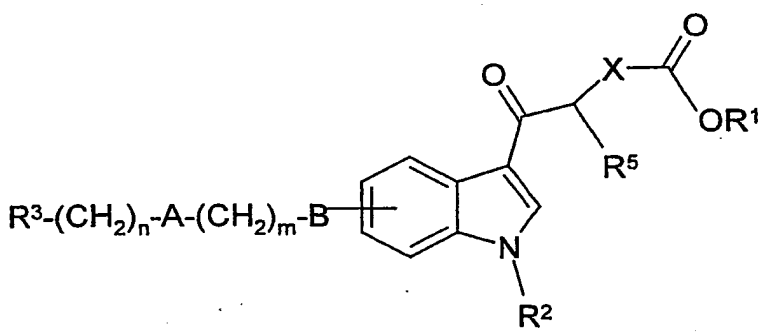
A	is NH,	
n	is 0,	
m	is 3 or 4 and	
R^3	is Het	



IVe

;

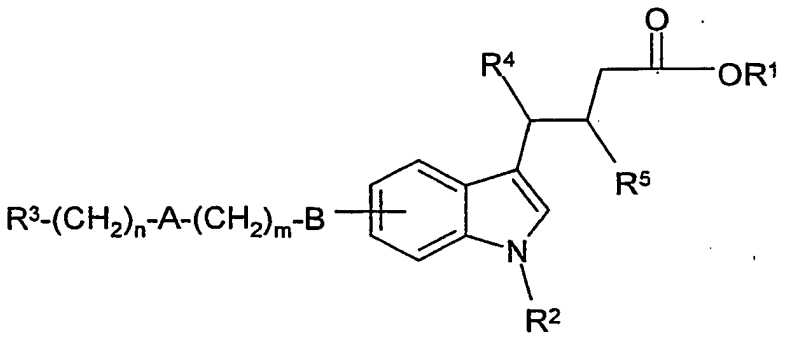
in IVf	X	is methylene, which is unsubstituted or substituted by Ar,
	R^2	is H,
	R^5	is H oder Ar and
	R^4	is oxo



IVf

;

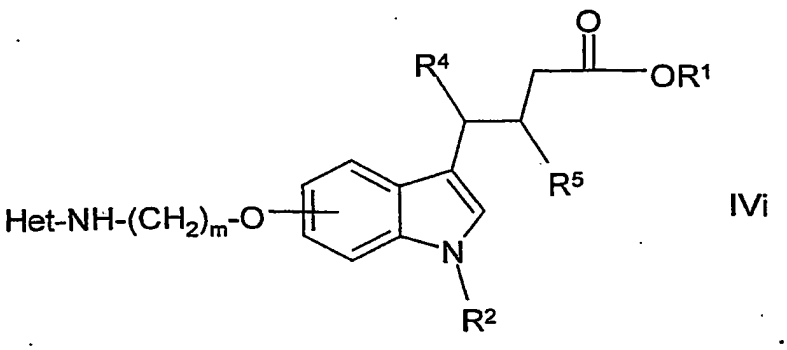
in IVg	X	is methylene,



IVg

;

	in IVh	X	is methylene,
		R^4	is H or Ar,
		R^5	is H or Ar and
		R^2	is H;
	in IVi	X	is methylene,
		R^4	is H or Ar,
		R^5	is H or Ar,
		B	is O,
		A	is NH,
		n	is 0,
		m	is 3 or 4
		R^3	is Het and
		R^2	is H



IVi

32. A method according to Claim 30 wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is a compound selected from the group consisting of

3-phenyl-3-{6-[3-(pyridine-2-ylamino)-propoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-{6-[4-(pyridine-2-ylamino)-butoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-{5-[4-(pyridine-2-ylamino)-butoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-{5-[3-(pyridine-2-ylamino)-propoxy]-1H-indole-3-yl}-propionic acid;

3-phenyl-3-[6-(pyridine-2-yl-amidocarboxymethoxy)-indole-3-yl]-propionic acid;

3-phenyl-3-[6-(benzimidazole-2-yl-amidocarboxymethoxy)-indole-3-yl]-propionic acid;

3-phenyl-3-[6-(imidazole-2-yl-amidocarboxymethoxy)-indole-3-yl]-propionic acid or

3-Benzo[1,2,5]thiadiazol-5-yl-3-{6-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-1H-indol-3-yl}-propionic acid

as well as their physiologically acceptable salts and solvates

33. A method of Claim 30 werein wherein the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor is

3-phenyl-3-{6-[3-(pyridine-2-ylamino)-propoxy]-1H-indole-3-yl}-propionic acid or

3-Benzo[1,2,5]thiadiazol-5-yl-3-{6-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-1H-indol-3-yl}-propionic acid

34. A method of Claim 30 wherein said amount is from about 0.5 µg to 5 mg

35. A method of Claim 30 wherein said eye disease is diabetic retinopathy

36. A method of Claim 30 wherein said eye disease is macular degeneration

37. A method of Claim 30 wherein said eye disease is myopia

38. A method of Claim 30 wherein said eye disease is ocular histoplasmosis

39. A method for prophylaxis and/or treatment of diseases of the eye of a patient resulting from angiogenesis in the eye comprising injecting into the subTenon's space of the eye of said patient a composition comprising nanoparticles containing a therapeutically effective amount of an $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ inhibitor sufficient to inhibit angiogenesis of the eye

40. A method of Claim 39 characterized in that the nanoparticles contain a biocompatible polymer

41. A method of Claim 39 characterized in that the nanoparticles contain a biodegradable polymer

42. A method of Claim 41 characterized in that the polymer is poly(lactic acid) (PLA), poly(glycolic acid) (PGA), polycaprolactone (PCL), a copolymer of lactic acid and glycolic acid (PLGA), a copolymer of lactic acid and caprolactone, polyepsilon caprolactone, polyhyroxy butyric acid, a poly(ortho)ester, a polyurethane, a polyanhydride, a polyacetal, a polydihydropyran or a polycyanoacrylate

43. A method of Claim 39 characterized in that the composition comprise a liquid medium wherein the nanoparticles are being dispersed thereby

forming a colloidal suspension

44. A method of Claim 39, characterized in that the nanoparticles have a diameter from about 10 nm to about 500 nm

45. A method of Claim 39 characterized in that the nanoparticles have a diameter from about 100 nm to about 200 nm

46. A method of Claim 39 characterized in that the nanoparticles have been prepared by solvent displacement

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 03/01369

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/12 A61K31/535 A61K31/353 A61K31/405 A61K9/51
A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 28473 A (ALCON UNIVERSAL LTD ;MARSH DAVID ALLEN (US); CLARK ABBOT F (US); Y) 26 April 2001 (2001-04-26) page 1, line 1 - line 12; claims 17,19,23 page 13, line 13 - line 14	1-46
P,Y	WO 02 41910 A (MERCK PATENT GMBH ;LANG ULRICH (DE); BENDER HANS MARKUS (DE); HAUN) 30 May 2002 (2002-05-30) claims	1-46
Y	US 6 001 961 A (GOODMAN SIMON ET AL) 14 December 1999 (1999-12-14) column 2, line 39 - line 42; claims column 2, line 56 - line 67 & EP 0 770 622 A 2 May 1997 (1997-05-02) cited in the application	1-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2003	25/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/CR 03/01369

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 35949 A (MERCK PATENT GMBH ;GOODMAN SIMON (DE); MAERZ JOACHIM (DE); RADDATZ) 20 August 1998 (1998-08-20) cited in the application page 3, line 10 - line 15; claims page 5, last paragraph	1,12-20
Y	WO 00 26212 A (MERCK PATENT GMBH ;GOODMAN SIMON (DE); MAERZ JOACHIM (DE); RADDATZ) 11 May 2000 (2000-05-11) cited in the application page 3, line 5 - line 10; claims page 5, last paragraph	1,21-29
Y	WO 01 58893 A (MERCK PATENT GMBH ;GOODMAN SIMON (DE); GOTTSCHLICH RUDOLF (DE); WI) 16 August 2001 (2001-08-16) cited in the application page 2, line 24 -page 3, line 8; claims page 6, paragraph 1	1,30-38
Y	WO 97 03657 A (UNIV BROWN RES FOUND) 6 February 1997 (1997-02-06) cited in the application the whole document	1,39-46

INTERNATIONAL SEARCH REPORT

Inte onal application No.
CT/EP 03/01369

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/EP 03/01369

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0128473 A	26-04-2001	AU 7854800 A	30-04-2001
		CA 2383572 A1	26-04-2001
		EP 1221918 A1	17-07-2002
		JP 2003511204 T	25-03-2003
		TW 467740 B	11-12-2001
		WO 0128473 A1	26-04-2001
		US 6413245 B1	02-07-2002
WO 0241910 A	30-05-2002	AU 3840802 A	03-06-2002
		WO 0241910 A2	30-05-2002
US 6001961 A	14-12-1999	DE 19534177 A1	20-03-1997
		AT 189461 T	15-02-2000
		AU 717574 B2	30-03-2000
		AU 6558096 A	20-03-1997
		BR 9603751 A	02-06-1998
		CA 2185489 A1	16-03-1997
		CN 1149588 A	14-05-1997
		CZ 9602643 A3	16-04-1997
		DE 59604363 D1	09-03-2000
		DK 770622 T3	03-07-2000
		EP 0770622 A2	02-05-1997
		ES 2144179 T3	01-06-2000
		GR 3033293 T3	29-09-2000
		HU 9602507 A2	28-08-1997
		JP 9132593 A	20-05-1997
		NO 963853 A	17-03-1997
		PL 316071 A1	17-03-1997
		PT 770622 T	31-07-2000
		RU 2157379 C2	10-10-2000
		SI 770622 T1	31-08-2000
		SK 116796 A3	10-05-2001
		TR 970294 A2	22-04-1997
		ZA 9607768 A	07-04-1997
WO 9835949 A	20-08-1998	DE 19705450 A1	20-08-1998
		AT 225776 T	15-10-2002
		AU 735313 B2	05-07-2001
		AU 6620698 A	08-09-1998
		BR 9807345 A	21-03-2000
		CN 1252064 T	03-05-2000
		CZ 9902875 A3	17-11-1999
		DE 59805895 D1	14-11-2002
		DK 964856 T3	10-02-2003
		WO 9835949 A1	20-08-1998
		EP 0964856 A1	22-12-1999
		ES 2183332 T3	16-03-2003
		HU 0001138 A2	28-05-2001
		JP 2001511789 T	14-08-2001
		NO 993901 A	12-10-1999
		PL 335101 A1	10-04-2000
		PT 964856 T	28-02-2003
		RU 2187506 C2	20-08-2002
		SI 964856 T1	30-04-2003
		SK 107199 A3	16-05-2000
		TR 9901962 T2	21-12-1999
		US 2001021709 A1	13-09-2001
		ZA 9801178 A	21-05-1999

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/Er 03/01369

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0026212 A	11-05-2000	DE 19850131 A1	04-05-2000
		AU 754280 B2	14-11-2002
		AU 6471699 A	22-05-2000
		BR 9914893 A	17-07-2001
		CA 2348391 A1	11-05-2000
		CN 1329610 T	02-01-2002
		CZ 20011515 A3	15-08-2001
		WO 0026212 A1	11-05-2000
		EP 1124824 A1	22-08-2001
		HU 0104800 A2	29-07-2002
		JP 2002528544 T	03-09-2002
		NO 20012108 A	27-04-2001
		PL 347246 A1	25-03-2002
		SK 5532001 A3	03-12-2001
WO 0158893 A	16-08-2001	DE 10006139 A1	16-08-2001
		AU 3166401 A	20-08-2001
		BR 0108154 A	21-01-2003
		CA 2399813 A1	16-08-2001
		CN 1398264 T	19-02-2003
		CZ 20022616 A3	16-10-2002
		WO 0158893 A2	16-08-2001
		EP 1254133 A2	06-11-2002
		NO 20023770 A	09-08-2002
		US 2003045728 A1	06-03-2003
WO 9703657 A	06-02-1997	US 6143211 A	07-11-2000
		AU 718482 B2	13-04-2000
		AU 6505096 A	18-02-1997
		AU 714584 B2	06-01-2000
		AU 6762396 A	18-02-1997
		EP 0844871 A1	03-06-1998
		EP 0840623 A1	13-05-1998
		JP 11510142 T	07-09-1999
		JP 2001513071 T	28-08-2001
		WO 9703702 A1	06-02-1997
		WO 9703657 A1	06-02-1997
		US 6235224 B1	22-05-2001
		US 2001042932 A1	22-11-2001